Remarks

Claims 1-4 and 7-15 were examined, 5-6 are withdrawn from consideration and claims 16-21 have been added. Claims 1-4 and 7-15 were rejected under 35 U.S.C. Section 112, first paragraph, as nonenabled. Claims 3, 4, 7, 8, 10, 11 and 15 were rejected under 35 U.S.C. Section 102(e) as being anticipated by U.S. Patent No. 6,156,303 issued to Russell et al. and claims 1-5, 7-11 and 15 were rejected under 35 U.S.C. Section 102(e) as anticipated by U.S. Patent No. 6,093,392 issued High et al. The rejections are believed to be overcome by the above amendment and are otherwise traversed for reasons discussed below.

I. OVERVIEW OF THE AMENDMENTS

Independent claims 1 and 3 have been amended to recite, in part, administering a preparation of rAAV virions "lacking the components necessary to form replication competent adenovirus." This amendment is supported in the Application at page 8, lines 10-15. No new matter has been added to these claims. Claim 12, has been amended accordingly. Amendment of these claims is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record.

Claims 16-21 have been added, of which claim 16 is in independent form. Claim 16 recites, in part, "expressing a heterologous nucleic acid in a mammalian subject" and administering "rAAV virion to said subject." Claim 17 depends from claim 16 and recites administration "by way of direct injection into a muscle cell". Claim 18 depends from claim 17 and recites that the "muscle cell is a skeletal muscle cell." New

claim 19 depends from claim 16 and recites administration "to a vascular conduit." New claims 20 and 21 depend from claim 19 and further define the vascular conduit. The new claims are supported in the Application at page 10 line 30 through page 14, line 2.

II. ENABLEMENT

A. Route of Delivery of rAAV

The Examiner has stated that "[t]he specification teaches using intramuscular (i.m.) administration for targeting muscle cells" but not any other route of administration that targets muscle cells. Office Action dated November 6, 2003 ("Office Action") at page 5. However, the present specification clearly sets forth procedures for targeting muscle cells by routes of administration other than direct injection. Applicants direct the Examiner's attention to the specification at page 5, line 16-18 and pages 12-13 where delivery of rAAV to the muscle via intravascular administration through isolated limb perfusion techniques is clearly described and enabled.

B. Use of Heterologous Nucleic Acids Other Than Factor IX

Applicant respectfully submits that the teachings and examples provided in the specification, in view of the knowledge in the art, provide sufficient guidance such that one of skill could indeed practice the claimed invention. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with the information known in the art, without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). In fact, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which the experiment should proceed, to enable the determination of how to practice a desired

embodiment of the claimed invention. *Ex parte Forman, supra; In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The Office Action alleges that the specification fails to provide sufficient guidance and/or factual evidence for one skilled in the art to use the full scope of the claimed invention. In particular, the Examiner stated that "[t]he breadth of the claimed methods embraces treating a variety of diseases and/or disorders . . . that are not taught by the prior art or the as-filed specification." Office Action at page 5. The Examiner further indicates that AAV "is too short for delivering some nucleic acid sequences, e.g., full-size of hFVIII cDNA, CFTR, and the dystrophin gene." Office Action at pages 7-8 (citing Hortelano et al., Art. Cells, Blood, Subs. and Immod. Biotech. Vol. 28, pages 1-24, 2000, and Wang et al., PNAS, Vol. 97, pages 13714-13719, 2000). However, Applicant is not required to prove the operability of each embodiment because "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." M.P.E.P. § 2164.08(B). Furthermore, it is axiomatic that a patent specification "need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 231 USPQ 81, 94 (Fed. Cir. 1986).

Nevertheless, evidence in the art demonstrates the universal applicability of the use of AAV-mediated gene therapy to a wide variety of diseases, *shows* that the claimed invention is enabled by Applicant's specification, and shows that the size of the AAV genome does not limit its ability to deliver heterologous genes. Experiments have shown that AAV virions can be used to deliver a number of different cDNA's that, when expressed, have a therapeutic effect. For example, Flotte et al., in a clinical protocol, state that "rAAV-CFTR mediates long-term, dose-dependent gene transfer to the

respiratory tract by direct bronchoscopic instillation, by aerosol, and by maxillary sinus administration." Flotte et al., Human Gene Therapy 14:93-128 at 97 (January 2004). Flotte et al. also state that AAV vectors expressed human alpha-1 antitrypsin from skeletal muscle and the vectors were "active in murine skeletal muscle for at least one year after a single injection." Id. at 99. In fact, several of the polypeptides listed in the application at pages 11-12 have been successfully delivered via rAAV, as discussed below.

Galeano et al., Diabetologia (2003) 46:546-555.

Galeano et al. demonstrate the use of rAAV to induce overexpression of human vascular endothelial growth factor-A (VEGF-A) in mice. AAV vectors encoding VEGF-A were injected intradermally into wound edges. This expression "enhanced wound repair ... including epidermal and dermal regeneration, thickness of granulation tissue, and formation of well-structured capillary vessels."

Song et al., Gene Therapy (2004) 11, 181-186.

Song et al. demonstrate rAAV-mediated delivery of human alpha-1 antitrypsin (hAAT) to nonobese diabetic mice. A solution of rAAV encoding hAAT was injected into the muscle of the mice. The rAAV injected group had less severe insulitis than the control group. Human AAT was continuously expressed in the injection sites from 10 to 32 weeks of age.

Skorupa et al., Experimental Neurology 160, 17-27 (1999).

Skorupa et al. demonstrate the expression of beta-glucuronidase (GUSB) to the brain via delivery of rAAV encoding GUSB. Mucopolysaccharidosis type VII (Sly disease) is a deficiency of GUSB, a representative neurodegenerative lysosomal storage disease. A solution containing rAAV encoding GUSB was injected into the brains of adult mice with Sly disease. Expression of GUSB at therapeutic levels was detected five months after a single injection.

Mochizuki et al., Gene Therapy (2004), 1-6.

Mochizuki et al. obtained phenyalanine hydroxylase (PAH)-deficient mice. The mice had phenotypic characteristics similar to human phenylketonuria. The mice were injected with rAAV5 encoding the enzyme PAH via the portal vein. Decreases in phenylalanine were observed 2-4 weeks after gene transfer and maintained for 40 weeks.

Tsai et al., Molecular Neuroscience (2003) 14(6):803-7.

Tsai et al. treated injured mice with rAAV encoding proinflammatory cytokine interleukin-1 receptor antagonist (IL-1ra). IL-1ra has been shown to attenuate ischemic inflammatory response and reduce infract volume and cerebral edema induced by ischemic brain injury. The rAAV-IL-1ra was injected into the brain and, seventy two hours later, higher levels of IL-1ra were detected in the treated anmials than the control animals. In addition, tissue damage was reduced.

U.S. Patent No. 6,221,349 issued to Couto et al., filed on July 30, 1999.

Couto et al. demonstrate that AAV vectors can be used to deliver DNA encoding Factor VIII. Couto et al. at column 29, line 19 through column 32, line 20. AAV vectors encoding Factor VII heavy and light chains were transfected into 293 cells. Column 27, line 57-66. The cells expressed Factor VIII at 4.6 ng/ml for one construct and 46 ng/ml for another construct. Column 28, line 1-10. In addition, mice coinjected with AAV encoding Factor VIII light chain and AAV encoding Factor VIII heavy chain "produced physiological levels of the active protein." Column 29, line 55 through column 30 line 2.

The above-discussed references illustrate that the rAAV genome is capable of delivering heterologous gene sequences other than Factor IX. One skilled in the art could readily determine, in view of the state of the art and the teachings of applicant's specification, how to select and use suitable nucleotide sequences for a given disease. Furthermore, although not required to establish enablement, multiple examples demonstrating dosages and routes of administration are provided in the specification.

C. Blood Clotting Efficiency

The Examiner stated that the specification does not enable use of "any HNA other than blood coagulation factors (e.g., Factor IX) to increase blood-clotting efficiency." Office Action at page 8. Applicants disagree and direct the Examiner's attention to page 12 of the specification which teaches the delivery of Factors VII, VIII, IX, X, XI, XIII and Protein C.

Contrary to the examiner's assertions, applicants have indeed adequately enabled the claimed invention in the specification such that one of skill in the art could make and use the invention without an undue amount of experimentation. Based on the foregoing, applicants submit that more than adequate evidence of enablement has been provided. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. Section 112, first paragraph, is respectfully requested.

III. NOVELTY

The examining attorney has rejected claims 3, 4, 7, 8, 10, 11 and 15 as anticipated by U.S. Patent No. 6,156,303 issued to Russell et al. ("Russel et al.") and claims 1-4 and 7-11 as anticipated by U.S. Patent No. 6,093, 392 issued to High et al. ("High et al.").

Independent claims 1, 3 and 16 recite, in part providing a preparation of rAAV virions "lacking the components necessary to form replication competent adeno virus." This amendment is supported in the Application at page 8, lines 10-15. Both Russell et al. and High et al. teach preparing AAV virions by transfecting cells with adenovirus. As a result, the preparations taught by Russell et al. and High et al. would not be free of adenovirus.

Russell et al. state that "substantially purified", when used in reference to an AAV nucleic acid molecule, means that the nucleic acid molecule comprising the viral genome is free from the relevant viral particle." Russell et al. at column 6, lines 4-8. However, Russell et al. teach that such a "substantially purified nucleic acid molecule can be prepared using routine methods such as gradient centrifugation following disruption of the viral particle." Id. at column 6, lines 5-11. Russell et al. also teach that heating AAV virions following centrifugation can "inactivate any contaminating adenovirus." Id. at column 19, lines 32-35. Thus, Russell et al. recognize that contaminating adenovirus may still be present following centrifugation and do not teach a preparation of AAV virions lacking the components necessary to form replication competent a adenovirus.

High et al. teach preparing rAAV by transfecting AAV-Factor IX plasmid "into human embryonic kidney (293) cells infected with an E1-deleted adenovirus." High et al. at column 13, lines 44-47. The AAV-hF.IX is then purified by "four rounds of CsCl density gradient centrifugation." Id. at column 13, lines 57-60. High et al. further teach that: "Purified AAV-hFIX routinely lacked *detectable* amounts of contaminating adenovirus when analyzed by transduction of 293 cells followed by staining for alkaline phosphatase or ß-galactosidase." Id. at column 14, lines 7-10 (emphasis added). However, "[w]ild-type AAV was detected at <1 infectious unit per 10^9 genomes of AAV-hFIX." Id. at column 14, lines 11-12.

Both High et al. and Russell recognize that rAAV virions will be contaminated with some level of adenovirus, whether a minute amount or inactive. A virus's ability to replicate itself when placed in a host cell make any level of contamination unacceptable

and potentially harmful to a host organism. Thus, High et al. and Russell et al. do not disclose or enable rAAV6 free of adenovirus and amended claims 1 and 3 are patentable over the two reference.

Amended claims 1 and 3 are also patentable over High et al. and Russell et al. because of the unexpectedly high expression levels seen with the administration of rAAV6 free of adenovirus. High et al. disclose an expression level plateau of "200 to 350 ng hF.IX ml of mouse plasma" five to seven weeks following injection of 2×10^{11} viral vector genomes per mouse. High et al. at column 16, lines 53-59.

Applicant achieved circulating plasma concentrations of hF.IX of 185 ng/mL three weeks post injection, 190 ng/mL seven weeks post injection and 300 ng/mL eleven weeks post injection. Application at page 19 line 29 through page 20 line 7. This expression level was achieved with a dose of 2×10^{11} viral vector genomes/kg. Application at page 19, lines 19-21. Based on the average mouse size of about 25 grams, this dose is about 1/40 of the dose use to achieve the same expression level in High et al. (2×10^{11} viral vector genomes/kg x 25 grams/mouse x 1 kg/1000 grams). Applicant believes that contamination with adenovirus leads to expression of immunogenic proteins, causing a reduction in the expression level of the therapeutic peptide. Accordingly, Applicant claims, which recite administering rAAV6 virions "lacking components necessary to form replication competent adenovirus" are patentable over the cited references.

IV. SUMMARY

The application provides enablement commensurate in scope with its claims. Applicant has demonstrated that rAAV virions can be used to express a variety of heterologous genes. Applicant submits that nothing more is required in order to enable the claimed invention. The claims are patentable over the cited references, Russell et al. and High et al., because the references do not disclose the administering rAAV virions lacking adenovirus.

Accordingly, the Applicant believes that the application is now in condition for allowance. In the event the examining attorney finds any remaining impediment to a prompt allowance of the claims which could be clarified or satisfied by a telephonic discussion or interview, the examining attorney is respectfully requested to contact Christina Thomson by telephone at (510)748-7208, or by fax at (510)748-7368.

Respectfully submitted,

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